Institutional Review Boards

Purpose and Challenges

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Institutional review boards (IRBs) or research ethics committees provide a core protection for human research participants through advance and periodic independent review of the ethical acceptability of proposals for human research. IRBs were codified in US regulation just over three decades ago and are widely required by law or regulation in jurisdictions globally. Since the inception of IRBs, the research landscape has grown and evolved, as has the system of IRB review and oversight. Evidence of inconsistencies in IRB review and in application of federal regulations has fueled dissatisfaction with the IRB system. Some complain that IRB review is time-consuming and burdensome without clear evidence of effectiveness at protecting human subjects. Multiple proposals have been offered to reform or update the current IRB system, and many alternative models are currently being tried. Current focus on centralizing and sharing reviews requires more attention and evidence. Proposed changes to the US federal regulations may bring more changes. Data and resourcefulness are needed to further develop and test review and oversight models that provide adequate and respectful protections of participant rights and welfare and that are appropriate, efficient, and adaptable for current and future research.

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ABBREVIATIONS: DHHS = Department of Health and Human Services; FDA = US Food and Drug Administration; IRB = institutional review board; NIH = National Institutes of Health; OHRP = Office of Human Research Protections

Institutional review boards (IRBs) or equivalent bodies provide a core protection for human participants in biomedical and behavioral research in the United States and > 80 other countries around the world.¹ IRBs are charged with providing an independent evaluation that proposed research is ethically acceptable, checking clinical investigators' potential biases, and evaluating compliance with regulations and laws designed to protect human subjects.

Independent review of clinical research by an IRB is required for US studies funded by the Department of Health and Human Services (DHHS) and other US federal agencies, as well as for research testing interventions—such as drugs, biologics, and devices—that are under the jurisdiction of the US Food and Drug Administration (FDA) (Table 1^{2,3}). US research institutions can and often do extend federal regulatory requirements to all of their human subjects research. Research conducted outside of the

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TABLE 1] Selected US Regulatory Requirements for IRBs (Paraphrased)

Regulation	Requirements
Membership (45CFR.46 107; 21CFR.56.107)	At least 5 members of varying backgrounds, both sexes, and > 1 profession
	At least 1 scientific member, 1 nonscientific member, and 1 unaffiliated member
	Members sufficiently qualified through diverse experience and expertise to safeguard subjects' rights and welfare and to evaluate research acceptability related to laws, regulations, institutional commitments, and professional standards
	At least 1 member knowledgeable about any regularly researched vulnerable groups
	Members report and recusal for conflicts of interest
Functions/operations (45CFR.46 108; 21CFR.56.108)	Ad hoc experts as needed
	Follow written procedures for initial and continuing review and for any changes and amendments
	Written procedures for reporting unanticipated problems, risks, and noncompliance
Review (45CFR.46 109; 21CFR.56.109)	Quorum of majority at convened meetings. Approval requires majority vote
	Authority to approve, require modifications of, or disapprove research
	Require informed consent and documentation (or approve a waiver ¹)
	Notify investigators in writing
Criteria for approval (45CFR.46 111; 21CFR.56.111)	At least annual continuing review
	IRB should determine that risks are minimized; risks are reasonable in relation to anticipated benefits, if any, and the importance of the expected knowledge; subject selection is equitable and attention to vulnerable populations; informed consent will be sought and documented; adequate provisions for monitoring; adequate provisions to protect confidentiality; additional safeguards for subjects vulnerable to coercion or undue influence
Authority (45CFR.46. 113; 21CFR.56.113)	Institutional officials cannot approve research that is disapproved by the IRB (45CFR.46 only)
	The IRB can suspend or terminate research for serious harm or noncompliance
Records (45CFR.46. 115, 21CFR.56.115)	Records of research proposals, meetings, actions, correspondence, members, and so forth

CFR = Code of Federal Regulations; IRB = institutional review board.

United States but funded by the US government is subject to the same US federal regulations and so requires IRB review or equivalent protections.⁴ Research conducted outside of the United States, not under an investigational new drug that submits data to the FDA for a new drug or biologic license application, must comply with Good Clinical Practice guidelines, which include review and approval by an independent review committee and informed consent.⁵ Regulations and laws in many other jurisdictions around the world also require review by an independent research ethics committee or IRB.⁶ Regulatory bodies in the European Union, Japan, United States, Canada, Australia, and Nordic countries, among others, follow Good Clinical Practice guidelines such as those delineated by the International Conference on Harmonisation, which require approval by an independent ethics committee or IRB.⁷ IRBs or research ethics committees, composed of a group of people independent of the specific research, review proposed

research plans and related documents before a study can begin and then periodically (usually annually) for the study duration. The goal of IRB review is to assure that the rights and welfare of participating research subjects will be adequately protected in the pursuit of the proposed research study. To be ethically acceptable and comply with regulatory requirements, the IRB determines that risks to subjects are minimized and reasonable in relation to the importance of the knowledge the study is expected to produce, that the process and outcomes of subject selection are fair (including delineated inclusion and exclusion criteria), and that there are adequate plans for obtaining informed consent.

History of IRBs in the United States

Recognizing that review by impartial others might mitigate conflicting differences in the ethical responsibilities of physician-investigators to research subjects from those of physicians to their patients and, thus, help to

protect the rights and welfare of research subjects, James Shannon, MD, Director of the National Institutes of Health (NIH), in 1965 proposed that all NIH research involving human subjects be evaluated by an impartial panel of peers to ensure its ethical integrity. His idea derived, at least in part, from a model that began at the NIH Clinical Center when it opened in 1953, which was a model of group peer review for research involving healthy volunteers.¹ In 1966, US Public Health Service policy requirements for ethical review, which were expanded to all Department of Health Education and Welfare (the DHHS predecessor) research by 1971, were not well enforced.¹ Regulations for the protection of human subjects for DHHS, published in 1974 (45CFR.46), included a requirement for group ethics review and the term “institutional review board” was introduced. The World Medical Association also introduced review by an independent committee for oversight of science and ethics into the 1975 revision of the Declaration of Helsinki.⁸ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established by the US Congress after revelations of the US Public Health Service syphilis studies at Tuskegee, authored the Belmont Report which explicated ethical principles underlying the conduct of human subjects research.⁹ The Commission’s contributions, including integration of the Belmont principles, were incorporated into updated US regulations in 1981. The 1981 DHHS regulations were subsequently adopted by 16 federal agencies (not including the FDA) in 1991 as the Common Rule. The FDA required an IRB beginning in 1981 (Title 21 Code of Federal Regulations, part 56), although some investigators funded by pharmaceutical companies already used oversight committees.¹⁰ The most extensive proposed changes to the Common Rule since 1991 were issued by the DHHS in an Advance Notice of Proposed Rule Making in 2011 in an effort to enhance protections and efficiency.^{11,12} Public comments were solicited and a Notice of Proposed Rulemaking is under development, but as of this writing has not been published (Fig 1).

US regulations at 45CFR.46 subpart E and 21CFR.56.106 require IRBs to be registered with the DHHS Office of Human Research Protections (OHRP), which is responsible for monitoring compliance with the Common Rule. Research institutions that receive DHHS funds file with OHRP an assurance that the institution will comply with federal regulations, called a Federal Wide Assurance.¹³ Each assurance has to include at least one internal or external IRB registered with OHRP. The

FDA requires registration of IRBs but does not require prospective assurances of compliance; sponsors and investigators include evidence of IRB review when they submit data to the FDA.

Changes to Research

At the time that IRBs were codified in regulation, single-site clinical research was the predominant paradigm. Advances in knowledge, technology, and resources over the subsequent decades have significantly changed the face of research. Growth in public and private spending^{14,15} as well as evolving scientific opportunities have created novel challenges for IRBs. The majority of clinical trials are now multisite, and some include > 100 sites, often with sites in multiple countries.¹⁶ In addition to multicenter and multinational research, IRBs review, for example, proposals for research with stored samples and data, cell-based and stem cell therapies, emergency research, social science research, and community-based research. IRBs operate under the same regulatory structure and use similar procedures despite a wide range of types of research posing disparate risks to subjects’ rights and welfare. Furthermore, the complexity of oversight has changed with the development of new entities involved in clinical research, such as contract research organizations, data and safety monitoring committees, clinical trial coordinating centers, accrediting associations, and commercial IRBs, among others.

Changes to IRBs

Concurrently, the number of, investment in, and responsibilities of IRBs have continued to increase. Most research institutions, universities, and health-care facilities have at least one IRB, and the majority has more than one.¹⁷ In addition, there are a number of independent or commercial IRBs.¹⁸ Increasingly, IRBs are tasked with responsibilities beyond those required by federal regulation, including, for example, review of conflicts of interest, compliance with privacy regulations, training of investigators, scientific review, and monitoring of clinical trial registration, among others. IRBs do indeed have responsibility for reviewing the science to assess the soundness of the design and the risks and benefits of the proposed research, however, many institutions have a separate scientific review process that precedes and complements IRB review.

Dissatisfaction and concern about what is perceived as an expansive mission and bureaucracy of IRBs has also mounted. Investigators and others criticize the IRB system as dysfunctional and “more concerned with

Figure 1 – Timeline of regulations and guidance regarding IRB review. ANPRM = Advance Notice of Proposed Rule Making; DHEW = US Department of Health, Education, and Welfare; DHHS = Department of Health and Human Services; FDA = US Food and Drug Administration; IRB = institutional review board; NIH = National Institutes of Health.

protecting the institution than research participants.”¹⁹ Some claim that IRBs are overburdened²⁰ and overreaching. Researchers, institutions, and some IRB members complain about burden: excessive paperwork, inflexible interpretation of regulatory requirements, attention to inconsequential details, and “mission creep”—the expanding obligations of IRBs that seem to have little to do with protection of research participants.²¹ Fear of regulatory admonition has fueled a focus on compliance with regulations.²² Some perceive the excessive or “hyper” regulation as seriously affecting or stifling research productivity and adding cost without adding meaningful protections for participants.^{23,24} Clinical investigators complain that the IRB review process is inefficient and delays their research for what seem like minor modifications.²⁵ The public hears about problems and fears that research might be unsafe and existing protections ineffective or inadequate.^{26,27}

Charles McCarthy, the first director of the US Office for Protection from Research Risks (the OHRP predecessor) noted, “[IRBs] have become more insightful and sophisticated... But unless [the Human Research Protection System] is considered to be an evolving and expanding mechanism, adapting to the problems of each period of history, it is in danger of becoming fossilized and ineffective.”²⁸ Flexibility and adaptability are important characteristics not usually attributed to IRBs. The challenge is how to evolve, expand, and adapt IRBs to the current exigencies of research in a rational and meaningful way. As noted by Cohen and Lynch,²⁹ the system is “ripe for a major course correction.”

Reform: Needs, Attempts, and Challenges

Recognition of the need for a robust system of protecting human research subjects within the changing research landscape has led to various proposals for reform and suggestions for alternative models.³⁰⁻³⁵

Reform proposals offer changes to address some of the various factors that are problematic for IRBs and for those who use them. Yet, reform efforts have been somewhat paralyzed by the tension between those who find the current system inadequate and those who find it too overreaching.^{36,37} Nonetheless, many grant that multiple reviews for a single study are duplicative, lead to significant delays in research without adding meaningful protections, and can result in inconsistencies that bias the science.^{38,39} Additional reasons for considering reform of the current oversight system include inherent conflicts of interest, inadequate resources, the emergence of new research methodologies, and insufficient expertise of members, among others.⁴⁰ IRBs also grapple with how to respond to evolving research methods, and high profile cases in which regulators disagree with or disapprove of IRB decisions can fuel uncertainty and anxiety.^{41,42}

Various systems of pre-IRB review have gained traction as a way to improve IRB efficiency: Major issues and gaps can be identified and corrected through prereview before an IRB sees the proposal. Institutions are also adopting a framework that more explicitly recognizes the essential roles of the institution, investigators, and research teams in addition to IRBs in protecting human subjects.⁴³ Several alternatives to the traditional model of single IRB review or review at each site of a multisite study have been developed and tried (Table 2).⁴⁴⁻⁵³ Proposed revisions to the Common Rule include a recommendation for a single IRB of record for domestic multisite trials.⁹ More recently, the NIH called for comments on a draft proposal for a single IRB review for NIH-funded multisite trials.⁵⁴ NIH is also currently funding several empirical studies of central IRBs with the goal of informing policy development relevant to central IRBs.⁵⁵ Despite these significant efforts, many challenges remain in changing the process of IRB review, including questions of liability, cost structures,

TABLE 2] Alternative Models for IRB Review

Type	Explanation	Examples
Local IRB review	Single-site study or review at each site for single site or multisite studies	Most research institutions have ≥ 1 IRB at the site that review research conducted at that site.
Shared IRB review		
Reliance	An institution formally “relies” on the IRB of another institution for review of a particular study or set of studies.	Increasingly ≥ 1 site partner with another IRB through a reliance agreement. See, for example NIAID, CHOP, and others.
Shared review	Concurrent regional or central and local review	Indian Health Service
Centralized review		
Central IRB	Central IRB established to review all studies of a type, each site accepts the central review	National Cancer Institute’s Central IRB (2 adult, 1 pediatric, 1 cancer prevention and control)
		American Academy of Family Physicians National Research Network IRB
		Veterans Administration central IRB
	A group of institutions form an alliance and create a new central IRB to serve as IRB for group. OR An existing IRB is designated as the central IRB for all sites of a network.	Biomedical Research Alliance of New York (BRANY) The IRB at Massachusetts General Hospital is designated as IRB of record for all NINDS-funded NeuroNext institutions.
		One of the existing NIH intramural IRBs is designated as the central PHERRB for public health emergencies.
Independent/commercial	A freestanding IRB (not part of an institution) is employed to review single or multiple site studies.	Western IRB, Chesapeake IRB, many others
Federated model	Allows sites to choose among multiple options including reliance, shared review, local review, or facilitated review. All options include a commitment to sharing IRB submissions and determinations among study sites.	National Children’s Study (NICHD)

CHOP = Children’s Hospital of Philadelphia; NIAID = National Institute of Allergy and Infectious Diseases; NICHD = National Institute of Child Health and Human Development; NIH = National Institutes of Health; NINDS = National Institute of Neurological Disorders and Stroke; PHERRB = Public Health Emergency Research Review Board. See Table 1 legend for expansion of other abbreviation. (Adapted from the Alternative Models Table in “Summary of the 2006 National Conference on Alternative IRB Models: Optimizing Human Subject Protection.”³¹)

and incentives, and uncertainty about the relative merits of proposed models.⁵⁶

Need for Evidence

Reform proposals often recognize the need for data about what works and for creative and testable ways of achieving the appropriate combination of protecting the rights and welfare of participants with meaningful and efficient IRB review that promotes high quality, relevant, and timely research. Evidence about how well IRBs are functioning, how effective they are, and how they could be more efficient would provide useful guidance for reform efforts.⁵⁷ Existing studies describe IRB structure, process, or outcomes and show that IRB judgments are inconsistent, as is their application of a standard set of regulations.^{58,59} Practices and decisions vary between and within IRBs often without justification, including determinations about risk level, inclusion criteria, and

the appropriateness of methods of recruitment and consent.^{55,60} Despite complaints about inconsistency, independence and local evaluation make some IRB variation inevitable. Moreover, it is difficult to find a study or to identify metrics able to measure how effective IRBs are at ensuring the ethical conduct of research or protecting research participants.⁶¹ Improving effectiveness requires clear and measurable goals for IRBs and ethical justification for regulatory requirements.⁶²

Many of these factors converge for critics of the IRB system: growing requirements and costs,^{63,64} bureaucratic burden, vague goals, and limited evidence of effectiveness.

“The available evidence indicates that there are substantial direct and indirect costs associated with IRB oversight of research. IRBs also operate inconsistently and inefficiently, and focus their attention on paperwork and bureaucratic compliance. Despite their prevalence, there

is no empirical evidence that IRB oversight has any benefit whatsoever—let alone benefit that exceeds the cost.”⁶⁵

Both normative analysis and empirical evidence are needed to understand how to improve the current system and optimize protections for contemporary research. If the goal is primarily to protect research participants from risk, for example, then more analysis of what risks count and more empirical evidence about research risks would provide direction for how we are doing and where the gaps are. As Taylor⁶⁶ notes, “whether and how to protect is inescapably normative and inescapably empirical.” In its 2011 report *Moral Science: Protecting Human Participants in Human Subjects Research*, the President’s Commission recommended that federal agencies involved in the funding of human subjects research “develop systematic approaches to assess the effectiveness of human subject protections and expand support for research related to the ethical and social considerations of human subject protections.”⁶⁷

Centralizing IRB Review

Primarily driven by concerns about redundant review, burden, and delay, much attention has been given to the idea of single or central IRB review for multisite studies as an alternative to local IRB review at each site. Multiple reviews also have the possibility of jeopardizing the science by introducing bias.³⁷ Institutions participating in multisite studies are permitted by federal regulations⁶⁸ to use arrangements that centralize or share reviews, yet relatively few employ these options. Many proposals for reforming or updating guidance and regulations have recommended single or central review for multisite studies.^{10,28-31,35} Lingering resistance to adopting central or single review for multisite trials appears to be based on concerns about the importance of local context, local accountability and liability, discomfort with relinquishing control over the review, uncertainty about the quality of review by other IRBs, and logistical concerns such as cost-sharing.^{30,54} There is a paucity of data evaluating how single or central review compares to review at local sites regarding quality of review, satisfaction, resource use, or efficiency.

Conclusions

IRBs have an important role in protecting human research participants from possible harm and exploitation. Independent review by an IRB or equivalent is an important part of a system of protections aiming to ensure that ethical principles are followed and that adequate and appropriate safeguards are in place to protect subjects’ rights and welfare while they contribute to

ethically and scientifically rigorous research. Over the four decades since IRBs were codified into regulations, IRB review and oversight has developed and matured as part of a robust system that provides “substantial protections for the health, rights, and welfare of research subjects.”⁶⁹ However, during that same period, research methods and opportunities have evolved, the domains of oversight have expanded, and the research enterprise has grown and diversified. The rules, norms, procedures, and even articulation of the goals of IRB review have not kept pace. Although ethical principles underlying research with human subjects have not changed, their implementation and actualization requires refinement and adaptation to respond to changing scientific and social contexts. Data, creativity, regulatory flexibility, and continued dialogue are needed to optimize the implementation of principles and to help shape the future structure, organization, processes, and outcomes of review and oversight by IRBs and related players. These efforts will support progress in clinical research, public trust in the enterprise, and protection of the participants that make research possible.

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References

1. McCarthy C. The origins and policies that govern institutional review boards. In: Emanuel E, Grady C, Crouch R, Lie R, Miller F, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; 2008:541-550.
2. US Code of Federal Regulations. Title 45CFR, part 46. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>. Accessed January 5, 2015.
3. US Code of Federal Regulations. Title 21CFR, part 56. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>. Accessed January 5, 2015.
4. US Code of Federal Regulations. Title 45CFR.46.101 (h).
5. US Code of Federal Regulations. Title 21 CFR 312.120; guidance for industry and FDA staff FDA acceptance of foreign clinical studies not conducted under an IND frequently asked questions. US Food and Drug Administration website. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>. Accessed April 12, 2015.
6. US Department of Health and Human Services. Office of Human Research Protections (OHRP). International compilation of human subjects standards. US Department of Health and Human Services website. <http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html>. Accessed March 1, 2015.
7. ICH guidelines: E6. good clinical practice. International Conference on Harmonisation website. <http://www.ich.org/>

- products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html. Accessed February 2, 2015.
8. Riis P. Letter from...Denmark. Planning of scientific-ethical committees. *BMJ*. 1977;2(6080):173-174.
9. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: Department of Health Education and Welfare; 1979. DHEW Publication OS 78-0012 1978.
10. Bowen A. Models of institutional review board function. In: Emanuel E, Grady C, Crouch R, Lie R, Miller F, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; 2008:552-559.
11. Office of Human Subjects Protection. Advanced notice of proposed rulemaking (ANPRM) for revision to Common Rule. US Department of Health and Human Services website. <http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html>. 2011. Accessed February 10, 2015.
12. Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. *N Engl J Med*. 2011;365(12):1145-1150.
13. Office of Human Research Protections. IRBs and assurances. US Department of Health and Human Services website. <http://www.hhs.gov/ohrp/assurances/index.html>. Accessed February 2, 2015.
14. Office of Budget: appropriations history by institute/center (1938 to present). National Institutes of Health, Office of Budget website. http://officeofbudget.od.nih.gov/approp_hist.html. Accessed March 3, 2015.
15. Pharmaceutical R&D and the evolving market for prescription drugs. Congressional Budget Office website. <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/106xx/doc10681/10-26-drug&d.pdf>. 2009. Accessed March 3, 2015.
16. Mascette AM, Bernard GR, Dimichele D, et al. Are central institutional review boards the solution? The National Heart, Lung, and Blood Institute Working Group's report on optimizing the IRB process. *Acad Med*. 2012;87(12):1710-1714.
17. Association for the Accreditation of Human Research Protection Programs. *2013 Metrics on Human Research Protection Program Performance*. Washington, DC: Association for the Accreditation of Human Research Protection Programs; 2014.
18. Commercial institutional review boards (IRBs). Citizens for Responsible Care and Research website. <http://www.circare.org/info/commercialirb.htm>. Accessed March 3, 2015.
19. Fost N, Levine RJ. The dysregulation of human subjects research. *JAMA*. 2007;298(18):2196-2198.
20. Burman WJ, Reves RR, Cohn DL, Schooley RT. Breaking the camel's back: multicenter clinical trials and local institutional review boards. *Ann Intern Med*. 2001;134(2):152-157.
21. Gunsalus CK, Bruner EM, Burbules NC, et al. Mission creep in the IRB world. *Science*. 2006;312(5779):1441.
22. Weil C, Rooney L, McNeilly P, Cooper K, Borror K, Andreason P. OHRP compliance oversight letters: an update. *IRB*. 2010;32(2):1-6.
23. Infectious Diseases Society of America. Grinding to a halt: the effects of the increasing regulatory burden on research and quality improvement efforts. *Clin Infect Dis*. 2009;49(3):328-335.
24. Silberman G, Kahn KL. Burdens on research imposed by institutional review boards: the state of the evidence and its implications for regulatory reform. *Milbank Q*. 2011;89(4):599-627.
25. Whitney SN, Alcer K, Schneider C, McCullough LB, McGuire AL, Volk RJ. Principal investigator views of the IRB system. *Int J Med Sci*. 2008;5(2):68-72.
26. Lemonick M, Goldstein A, Park A. Human guinea pigs. *Time*. April 22, 2002.
27. Gilbert S. Trials and tribulations. *Hastings Cent Rep*. 2008;38(2):14-18.
28. McCarthy C. The origins and policies that govern institutional review boards. In: Emanuel E, Grady C, Crouch R, Lie R, Miller F, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; 2008:550.
29. Cohen IG, Lynch HF, eds. Introduction. *Human Subjects Research Regulation, Perspectives on the Future*. Cambridge, MA: MIT Press; 2014:2.
30. Association of American Medical Colleges. Alternative Models of IRB Review Workshop summary. Washington, DC: Department of Health and Human Services; 2005.
31. Summary of the 2006 National Conference on Alternative IRB Models: optimizing human subject protection. Association of American Medical Colleges website. <https://www.aamc.org/download/75240/data/irbconf06rpt.pdf>. November 2006. Accessed January 5, 2015.
32. Mascette AM, Bernard GR, Dimichele D, et al. Are central institutional review boards the solution? The National Heart, Lung, and Blood Institute Working Group's report on optimizing the IRB process. *Acad Med*. 2012;87(12):1710-1714.
33. Federman D, Hanna K, Rodriguez L, eds. *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, DC: National Academies Press; 2003.
34. Klitzman R, Appelbaum PS. Research ethics. To protect human subjects, review what was done, not proposed. *Science*. 2012;335(6076):1576-1577.
35. Wood A, Grady C, Emanuel EJ. Regional ethics organizations for protection of human research participants. *Nat Med*. 2004;10(12):1283-1288.
36. Kim S, Ubel P, DeVries R. Pruning the regulatory tree. *Nature*. 2009;457(29):534-535.
37. Check DK, Weinfurt KP, Dombeck CB, Kramer JM, Flynn KE. Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature. *Clin Trials*. 2013;10(4):560-567.
38. Ledford H. Human-subjects research: trial and error. *Nature*. 2007;448(7153):530-532.
39. Menikoff J. The paradoxical problem with multiple-IRB review. *N Engl J Med*. 2010;363(17):1591-1593.
40. Emanuel EJ, Wood A, Fleischman A, et al. Oversight of human participants research: identifying problems to evaluate reform proposals. *Ann Intern Med*. 2004;141(4):282-291.
41. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. *N Engl J Med*. 2013;368(25):e36.
42. Fanaroff JM. Ethical support for surfactant, positive pressure, and oxygenation randomized trial (SUPPORT). *J Pediatr*. 2013;163(5):1498-1499.
43. Speers M. Evaluating the effectiveness of institutional review boards. In: Emanuel E, Grady C, Crouch R, Lie R, Miller F, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; 2008:560-568.
44. Christian MC, Goldberg JL, Killen J, et al. A central institutional review board for multi-institutional trials. *N Engl J Med*. 2002;346(18):1405-1408.
45. National Cancer Institute Central IRB Initiative. National Cancer Institute website. <https://ncicirb.org/cirb>. Accessed March 1, 2015.
46. Graham DG, Spano MS, Manning B. The IRB challenge for practice-based research: strategies of the American Academy of Family Physicians National Research Network (AAFP NRN). *J Am Board Fam Med*. 2007;20(2):181-187.
47. Office of Research and Development. VA central institutional review board (IRB). US Department of Veterans Affairs website. <http://www.research.va.gov/programs/pride/cirb>. Accessed March 1, 2015.
48. BRANY institutional review board services. Biomedical Research Alliance of New York (BRANY) website. <http://www.branyirb.com>. Accessed February 3, 2015.
49. Kaufmann P, O'Rourke PP. Central institutional review board review for an academic trial network. *Acad Med*. 2015;90(3):321-323.
50. Transformation solutions: about us. WIRB-Copernicus Group website. <http://wcgclinical.com/about-us/transformational-solutions>. Accessed March 10, 2015.
51. Why choose Chesapeake IRB? Chesapeake IRB website. <https://www.chesapeakeirb.com>. Accessed March 10, 2015.

52. Tip sheet 24 relying on an external IRB. Association for the Accreditation of Human Research Protection Programs website. <http://www.aahrpp.org/apply/resources/tip-sheets?docSortBy=Updated&docFilterBy=&docStart=5>. Accessed March 10, 2015. See also <http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Pages/faq.aspx>, <https://irb.research.chop.edu/irb-reliance-agreements>, and others.
53. Slutsman J, Hirschfeld S. A federated model of IRB review for multisite studies: a report on the National Children's Study federated IRB initiative. *IRB*. 2014;36(6):1-6.
54. Request for comments on the draft NIH policy on the use of a single institutional review board for multi-site research. National Institutes of Health website. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>. Published December 3, 2014. Accessed March 2, 2015.
55. Empirical research on ethical issues related to central IRBs and consent for research using clinical records and data (R01). National Institutes of Health website. <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-14-002.html> and <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-15-002.html>. Accessed April 12, 2015.
56. Flynn KE, Hahn CL, Kramer JM, et al. Using central IRBs for multicenter clinical trials in the United States. *PLoS ONE*. 2013;8(1):e54999.
57. Coleman CH, Bouësseau MC. How do we know that research ethics committees are really working? The neglected role of outcomes assessment in research ethics review. *BMC Med Ethics*. 2008;9:6.
58. Abbott L, Grady C. A systematic review of the empirical literature evaluating IRBs: what we know and what we still need to learn. *J Empir Res Hum Res Ethics*. 2011;6(1):3-19.
59. Lidz CW, Appelbaum PS, Arnold R, et al. How closely do institutional review boards follow the common rule? *Acad Med*. 2012;87(7):969-974.
60. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA*. 2004;291(4):476-482.
61. Grady C. Do IRBs protect human research participants? *JAMA*. 2010;304(10):1122-1123.
62. Presidential Commission for the Study of Bioethical Issues. Further analysis and recommendations: recommendation 5. In: *Moral Science: Protecting Participants in Human Subjects Research*. <http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf>. 2011. Accessed February 10, 2015.
63. Wagner T, Murray C, Goldberg J, Adler J, Abrams J. Costs and benefits of the National Cancer Institute Central Institutional Review Board. *J Clin Oncol*. 2010;28(4):662-666.
64. Sugarman J, Getz K, Speckman JL, Byrne MM, Gerson J, Emanuel EJ; Consortium to Evaluate Clinical Research Ethics. The cost of institutional review boards in academic medical centers. *N Engl J Med*. 2005;352(17):1825-1827.
65. Hyman D. Institutional review boards: is this the least worst we can do? *Northwestern University Law Review*. 2007;101(2):749-774.
66. Taylor P. Introduction to part II—protection of vulnerable populations. In: Cohen G, Lynch H, eds. *Human Subjects Research Regulation, Perspectives on the Future*. Cambridge, MA: MIT Press; 2014:63.
67. Presidential Commission for the Study of Bioethical Issues. Recommendation 2. In: *Moral Science: Protecting Participants in Human Subjects Research*. <http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf>. 2011. Accessed February 10, 2015.
68. US Code of Federal Regulations at 45CFR.46 and 21CFR56.
69. Presidential Commission for the Study of Bioethical Issues. Executive summary. In: *Moral Science: Protecting Participants in Human Subjects Research*. <http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf>. 2011. Accessed February 10, 2015.